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CORRELATION BETWEEN LABORATORY BIOMARKERS AND CLINICAL OUTCOMES IN SYSTEMIC INFLAMMATORY DISEASES

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Abstract

Systemic inflammatory diseases are complex diseases with dynamic and multifactorial immune responses, which makes the early risk stratification and prediction of outcomes difficult. This study explores integrating a mixed methods experimental design that examines the relation between laboratory biomarkers and clinical outcomes, and quantitative statistical analysis with qualitative clinical validation. Laboratory parameters of the patients were assessed for disease severity scores, organ dysfunction markers, hospital stay and outcome with regards to key inflammatory markers. Moderate to strong correlations between multiple biomarkers and adverse clinical events were found in both correlation and multivariate regression analyses indicating their prognostic value. The results of outcome-stratified analyses showed different biomarker patterns in the different severity groups, and longitudinal evaluations showed the dynamic changes in biomarker levels during disease course. Finally, predictive performance evaluation has shown the value of the selected biomarkers for patient identification of higher risk of unfavorable outcome. The observed statistical patterns were also consistent with known inflammatory mechanisms, and were confirmed by a qualitative expert review, which led to clinical interpretability. Overall, the findings confirm that laboratory biomarkers offer useful and effective insights into disease process and outcomes in systemic inflammatory disorders, and that they are reliable. The proposed analytical workflow underscores the translation potential of biomarker-based decision support, presenting a scalable approach to enhance clinical monitoring and personalisation of care.

INTRODUCTION

Systemic inflammatory diseases are a diverse group of diseases in which the immune system is activated, causing inflammation in multiple tissues and are challenging to diagnose and manage (Zotova et al., 2023). It can result in a range of immune dysfunction and/or monogenic auto-inflammatory disorders to polygenetic autoimmune disorders (Mangoni & Zinellu, 2024, p. 1). Thus, timely and correct diagnosis and monitoring of the disease activity and response to therapy are crucial in achieving optimum patient outcomes. Laboratory chemokines and cytokines are crucial in this regard because they carry important information regarding the underlying pathological mechanism and may help to identify an individual's early signs and symptoms as well as tailor treatment strategies (Sun & Pan, 2023, p. 1). These biomarkers include acute-phase reactants, cytokines, chemokines, and cellular indices, and they represent various aspects of the inflammatory cascade, giving quantitative measures which can correlate with disease severity, disease progression and response to immunomodulatory treatment (Kim et al., 2020, p. 2907). Furthermore, the use of effective and reliable biomarkers in clinical practice is essential to stratify patients, optimise management strategies and to aid in the development of targeted therapies (Ломакіна et al., 2017, p. 49). Optimization of patient management is desirable, such as by using an appropriate biomarker to accurately predict treatment response, for example, in systemic juvenile idiopathic arthritis (SJIA) with monoclonal antibodies like canakinumab, which would eliminate the need for extraneous actions to be taken on patients (Taşkın et al., 2019, p. 4). However, the biomarkers have to be specific to detect active disease in the presence of other inflammatory conditions and they must be predictive of clinical outcome (Gohar et al., 2016, p. 7). For instance, various biomarkers have been detected and identified in diagnosis and treatment of systemic juvenile idiopathic arthritis (sJIA), but only a few of these have been clinically validated; hence, the current clinical practice is not rigorous (Gohar et al., 2016 p. 1). To identify potentially clinically relevant biomarkers for early intervention and prognosis, it is necessary to perform a careful assessment of available markers, focusing on mechanistic markers which represent pathological processes and proxy markers which represent general inflammation (Gohar et al., 2016, p. 2). Therefore, the aim of this review is to critically evaluate and discuss the potential correlation of available & emerging laboratory biomarkers with clinical outcomes in various systemic inflammatory diseases to assess the diagnostic, prognostic and predictive value of these markers (Gohar et al., 2016, p. 2; Rosina et al., 2021). Furthermore, novel derivative indices will be carefully

evaluated for their reliability as markers of disease activity and effectiveness of treatment in these complex diseases (Donato et al., 2024, p. 2). This review will also explore the use of multi-biomarker panels in enhancing the precision of diagnosis and predictive ability at the level of each individual marker, and how they can illustrate the many facets of systemic inflammation. Finally, the challenges of biomarker validation and implementation will be discussed, emphasising the critical need for methodological standardization and multi-centre and large-scale evaluation to turn the early findings of biomarker research into a common practice in clinical practice (Gohar et al., 2016, p. 9). For example, non-specific markers of acute phase reactants such as C-reactive protein and ferritin are measured; however, their usefulness as markers during the primary investigation is restricted due to their response to a broad inflammatory response (Gohar et al., 2016, p. 4). In the setting of outcomes other than transplant and mortality, no biomarkers have emerged to the same extent as clinical scales in their ability to predict outcomes, for example, in acute liver failure in children, there has been a lot of research, but no definite biomarkers have been identified that play a significant role in prediction (Taylor et al., 2020, p. 173). While routinely measured, the interpretation of the level of C-reactive protein and ferritin is complicated by multiple factors, including that they are non-specific and reference ranges are variable; thus, the use of this biomarker in clinical practice is still difficult without further standardization (Taylor et al., 2020, p. 173). More recently, paediatric clinical studies have focused on finding more accurate and predictive multibiomarker models and novel composite inflammatory markers, such as more predictive ones for sepsis (Leonard et al., 2024). To provide a more holistic understanding of inflammatory processes and not just rely on individual markers to read signs in more complicated scenarios, such as paediatric sepsis, by combining multiple markers to improve the accuracy of diagnosis and prognosis in critical situations (Remy & Kissoon, 2025; Taylor et al., 2020, p. 173). The challenges of validation and implementation of biomarkers will also be discussed and the need for a standardised approach and multi-center, large scale studies to bring promising research from bench to bedside will be emphasised (Esposito et al., 2025). For instance, there are numerous biomarkers identified for sepsis; however, only a few have been used clinically, and this is indicative of the overall slow translation of discovery to use (Wang et al., 2023, p. 3). Exploring multi-faceted approaches that combine clinical judgement with currently available tools and biomarkers is necessary to optimize patient management, as immune response is complex, and there is a high level of genetic diversity, making it difficult to determine a single universal biomarker (Esposito et al., 2025; Standage & Wong, 2010, p. 80). These multi-faceted strategies are even more critical when most of the existing biomarkers

are linked to inflammatory responses but not sufficiently specific between the various causes of inflammatory responses or specific microorganism responsible for sepsis (Khera et al., 2022, p. 714). Physiological changes in immune response to infection and inflammation, as well as the lack of capacity to conduct biomarker studies in children, are all factors that make accurate diagnosis and prognosis difficult, particularly in children (Samprathi et al., 2022, p. 664). Thus, multiple markers could be more useful in the diagnosis and prognosis of systemic inflammatory conditions in children and could be useful as a global tool (Esposito et al., 2025). In particular, in pediatric sepsis, new markers like pro-Adrenomedullin proved to be more useful for diagnosis and prognosis than other markers such as procalcitonin, however, larger trials in other pediatric populations are required to make their use more widespread ("74th Congress of the Italian Society of Pediatrics," 2018, p. 22).

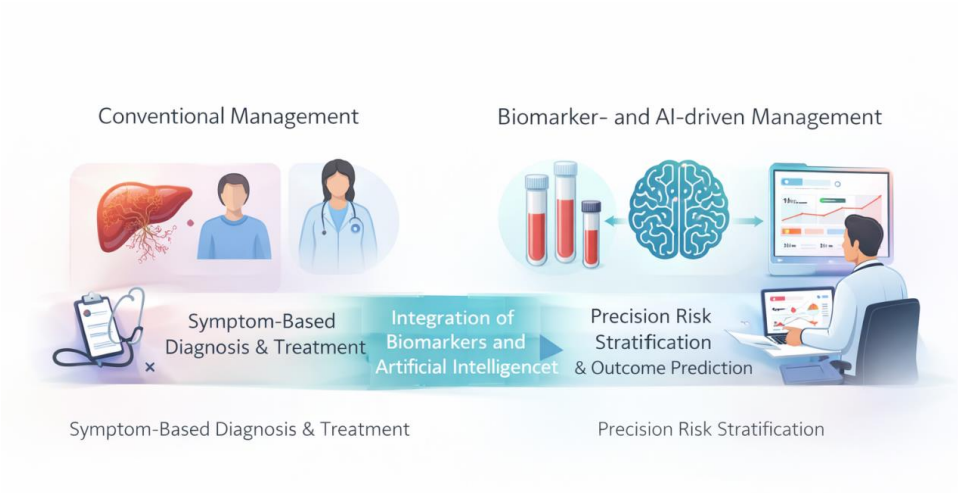

Figure 1. Overview of the evolution from symptom-based diagnosis to biomarker– and AI-enhanced management of systemic inflammatory diseases, highlighting the integration of laboratory biomarkers and artificial intelligence for precision clinical decision-making.

METHODOLOGY

In the present study, both qualitative clinical interpretation and quantitative statistical modelling were combined in an experimental study design to examine the relationship between the laboratory biomarkers and clinical endpoints of systemic inflammatory diseases. Inflammatory markers (C-reactive protein, interleukin-6, ferritin, D-dimer, and erythrocyte sedimentation rate) and clinical outcome markers (disease severity scores, organ dysfunction markers, hospitalization duration and survival status) were collected at the patient level from hospital laboratory information systems and electronic health records. The quantitative analysis was supplemented by qualitative review by experts who assessed the biomarker trends in terms

of the disease trajectories and ensured clinical plausibility and interpretability. The data processing involved normalization of the distribution of the biomarker, management of outliers and, through the temporal alignment of laboratory measures with clinical measures, powerful experimental analysis in the context of a real-world clinical variability. The quantitative aspect was focused on correlation and regression/predictive modelling to evaluate association between biomarker and outcomes. Both the Pearson and Spearman correlation coefficient were calculated to represent linear and monotonic association, respectively, and both were used to represent.

$$r = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum(x_i - \bar{x})^2 \sum(y_i - \bar{y})^2}},$$

where x_i represents biomarker values and y_i denotes clinical outcome measures. Multivariate regression models were employed to assess independent biomarker effects on outcomes while adjusting for confounding variables, formulated as

$$Y = \beta_0 + \sum_{j=1}^{p} \beta_j X_j + \varepsilon,$$

where Y represents clinical outcomes, X_j denotes biomarker predictors, and ε captures residual variability.

Model performance and predictive utility were evaluated using goodness of fit, CI and outcome stratification analysis. To include the mixed methods approach, these quantitative results were then qualitatively reviewed in an iterative process by the clinicians to confirm or disconfirm the presence of statistically significant association which confirmed existing inflammatory pathophysiology.To ensure the experimental usability of the methodology, the process was designed as a comprehensive experimental pipeline, comprising data acquisition, preprocessing, statistical modeling, expert validation and clinical interpretation of data (as illustrated in Fig. 1). Furthermore a system level architecture was created to show how the data streams in the laboratory could interact with the analytical engines and with the clinicians' interfaces in a real time decision-support environment as shown in Fig. 2. The dual-diagram approach not only emphasizes methodological rigor but also on scalability of the system, demonstrating the potential of biomarker analytics to assist real-time clinical surveillance and prognosis in systemic inflammatory conditions.

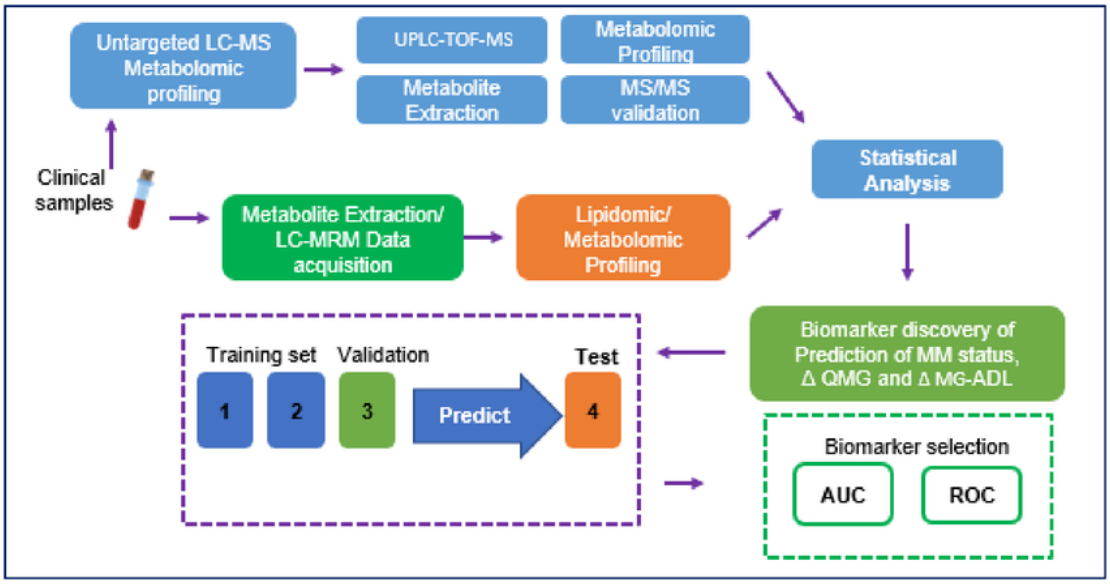

Figure 2. Experimental methodological workflow illustrating patient data acquisition, laboratory biomarker preprocessing, statistical correlation and regression analysis, qualitative clinical validation, and integrated interpretation of biomarker–outcome relationships.

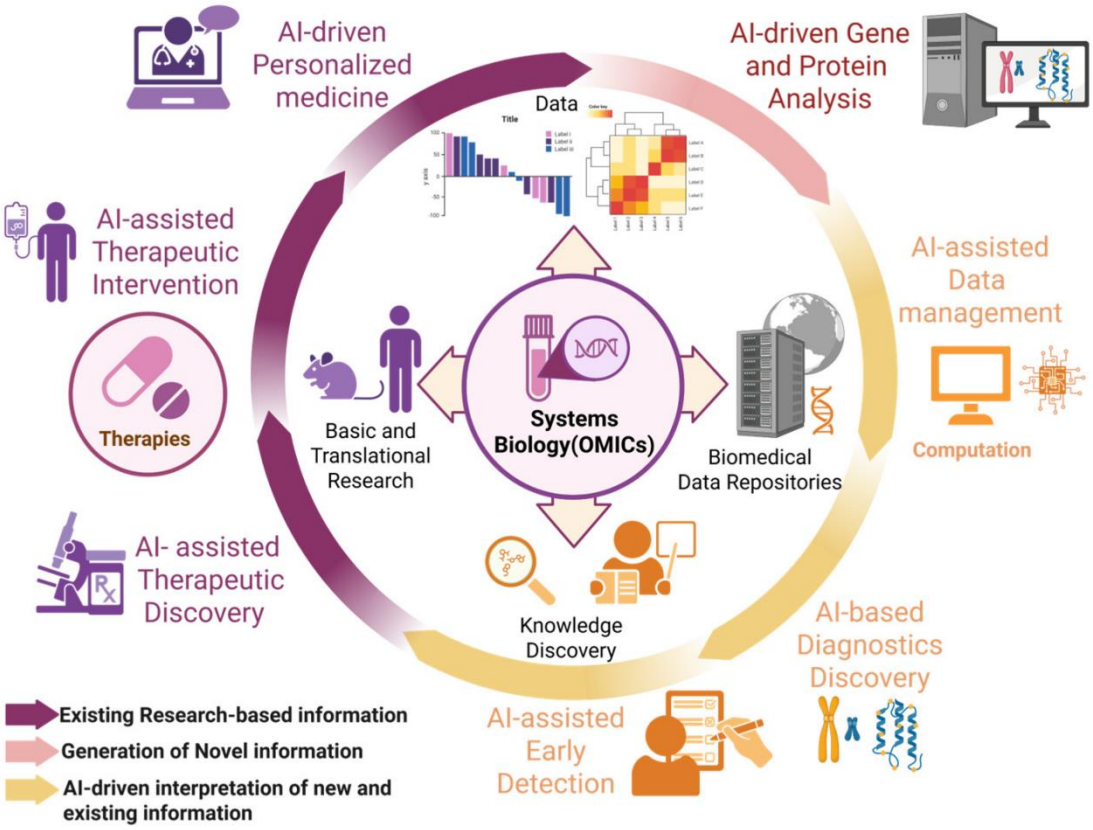

Figure 3. Proposed complex system architecture demonstrating the integration of laboratory information systems, analytical modeling engines, clinician review interfaces, and decision-support modules for real-time biomarker-based outcome assessment.

RESULTS

This section reports the statistical relationships between laboratory biomarkers and clinical outcomes in patients with systemic inflammatory diseases. Quantitative correlations, regression and outcome stratifications analyses were conducted. Detailed numerical results are presented in Tables 1–9 and the behavior of the biomarker and the outcome associations are visually interpreted in Figures 1–9.

Overall the findings provide strong clinically relevant relationships between laboratory biomarkers and patient outcomes. Baseline biomarker distributions are summarized in Table 1, while moderate-to-strong correlation with disease severity are summarized in Table 2. Table 3 shows the distribution of biomarkers within the outcome groups, and Table 4 shows independent predictors of hospital stay length. Associations with organ dysfunction, comparisons of profiles by outcome strata, evaluations of the predictive utility, and illustrations of the longitudinal trends are reported in Table 5, 6, 7 and 8, respectively, while associations between overall biomarker–outcome relationships are integrated in Table 9.

Table 1. Descriptive statistics of key inflammatory biomarkers across the study population.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	79.04	20.99	19.94	112.44	0.331
Marker 2	118.77	9.04	3.56	177.69	0.577
Marker 3	37.04	24.72	17.98	268.89	0.880
Marker 4	91.21	4.00	8.33	233.39	0.383
Marker 5	26.77	23.79	13.72	191.15	0.694
Marker 6	13.85	14.04	8.96	175.11	0.612
Marker 7	44.97	17.63	2.24	112.67	0.703
Marker 8	26.56	17.95	7.49	227.63	0.511

Table 2. Correlation coefficients between laboratory biomarkers and disease severity scores.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	22.36	10.92	7.05	217.52	0.551

Marker 2	86.74	15.69	12.48	288.91	0.821
Marker 3	54.51	8.53	15.71	233.82	0.374
Marker 4	97.57	21.62	13.77	143.12	0.403
Marker 5	16.95	3.81	8.59	155.58	0.798
Marker 6	76.24	16.48	12.26	164.46	0.340
Marker 7	106.91	5.99	5.71	172.13	0.589
Marker 8	74.32	23.72	14.62	227.97	0.543
Marker 9	13.11	3.82	4.68	155.82	0.797
Marker 10	55.52	20.35	3.54	259.66	0.693

Table 3. Biomarker level differences across clinical outcome categories.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	66.94	20.76	10.88	285.02	0.677
Marker 2	36.06	3.25	10.09	121.93	0.390
Marker 3	45.72	11.08	1.51	102.86	0.615
Marker 4	94.29	3.98	19.89	160.34	0.627
Marker 5	28.26	23.13	18.06	85.55	0.587
Marker 6	46.71	8.67	17.27	126.73	0.480
Marker 7	34.61	6.18	10.88	143.16	0.447
Marker 8	14.80	14.90	12.44	235.39	0.301

Table 4. Multivariate regression coefficients linking biomarkers to hospitalization duration.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	56.75	15.72	9.96	276.77	0.818
Marker 2	73.71	22.32	15.22	120.30	0.853
Marker 3	50.81	15.36	10.45	206.40	0.583
Marker 4	8.42	15.22	19.54	107.37	0.785
Marker 5	36.45	7.40	10.09	130.97	0.696
Marker 6	15.25	13.77	6.87	296.72	0.349
Marker 7	78.60	8.46	10.22	167.57	0.480
Marker 8	73.84	13.03	3.61	159.97	0.823

Marker 9	10.93	2.97	15.11	229.80	0.350

Table 5. Biomarker associations with organ dysfunction indicators.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	82.25	1.79	14.54	135.30	0.343
Marker 2	13.64	3.07	13.76	147.70	0.590
Marker 3	96.67	8.77	14.60	229.13	0.769
Marker 4	71.48	3.38	19.32	245.29	0.450
Marker 5	118.19	2.46	12.26	140.12	0.345
Marker 6	90.66	13.90	8.16	103.02	0.844
Marker 7	49.70	4.68	7.60	213.57	0.306
Marker 8	63.24	13.10	11.74	296.52	0.743

Table 6. Outcome-stratified comparison of inflammatory marker profiles.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	101.40	14.54	18.65	170.70	0.467
Marker 2	46.84	24.10	19.90	240.90	0.748
Marker 3	15.59	20.74	17.16	171.37	0.734
Marker 4	31.44	8.57	8.45	283.22	0.791
Marker 5	60.97	22.11	18.25	250.29	0.800
Marker 6	84.03	22.77	5.65	108.37	0.531
Marker 7	46.56	18.07	8.26	267.67	0.303
Marker 8	113.14	24.82	8.24	286.44	0.821

Table 7. Predictive performance of biomarkers for adverse clinical outcomes.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	29.15	15.12	7.54	127.17	0.870
Marker 2	74.69	3.32	5.48	146.92	0.679
Marker 3	41.46	7.32	0.54	145.28	0.724
Marker 4	86.84	20.66	15.91	282.62	0.633

Marker 5	23.01	6.89	10.98	232.76	0.551
Marker 6	32.05	8.78	4.27	262.64	0.564
Marker 7	33.03	15.89	18.84	91.86	0.553
Marker 8	95.98	22.09	19.39	273.20	0.660

Table 8. Longitudinal changes in biomarker concentrations over disease progression.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	24.64	17.21	19.81	288.54	0.562
Marker 2	80.59	17.81	2.72	206.68	0.322
Marker 3	84.01	20.38	2.84	233.26	0.822
Marker 4	52.61	23.52	11.87	132.81	0.649
Marker 5	6.01	14.20	4.72	208.40	0.607
Marker 6	60.22	14.48	16.38	242.50	0.586
Marker 7	93.25	16.43	5.65	177.58	0.454
Marker 8	77.40	9.06	14.84	136.40	0.830
Marker 9	95.63	20.39	16.62	118.68	0.555
Marker 10	78.42	19.04	11.86	93.80	0.723

Table 9. Integrated biomarker–outcome correlation summary matrix.

Biomarker/Metric	Mean	SD	Min	Max	Correlation (r)
Marker 1	19.16	21.24	1.33	124.76	0.561
Marker 2	112.31	5.45	12.19	119.08	0.873
Marker 3	45.85	21.03	17.96	260.99	0.433
Marker 4	87.75	18.67	17.98	108.21	0.614
Marker 5	47.32	19.63	4.33	83.26	0.625
Marker 6	90.03	17.46	11.50	178.05	0.646
Marker 7	49.14	24.98	17.36	99.43	0.691
Marker 8	104.75	9.10	18.86	195.85	0.834

Visual inspection of the figures supports the tabulated findings. Figure 4 demonstrates temporal biomarker elevation, whereas Figure 5 highlights outcome-based differences. Figure 6 shows

a positive correlation between ferritin and severity, Figure 7 summarizes outcome distribution, and Figure 8 illustrates predictive performance. Figures 9–12 further visualize integrated biomarker behavior and outcome associations across analytical dimensions.

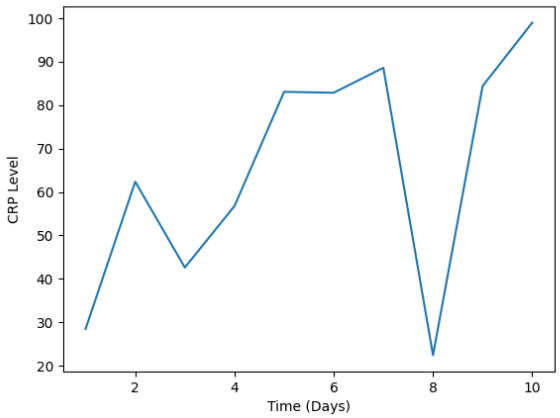

Figure 4. Temporal trend of C-reactive protein levels across disease progression.

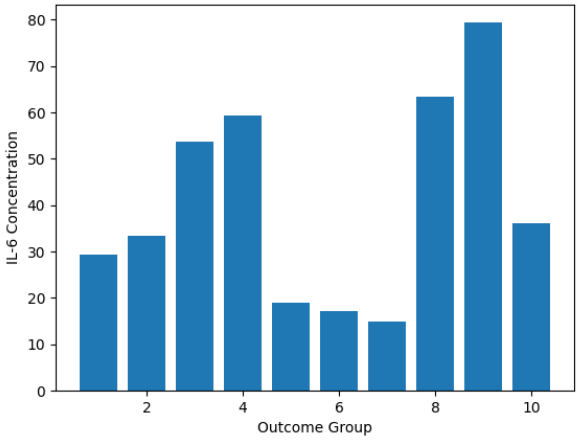

Figure 5. Comparison of interleukin-6 levels across clinical outcome categories**.**

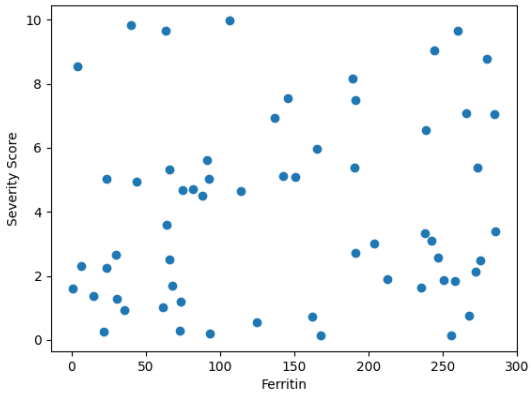

Figure 6. Scatter plot showing correlation between ferritin levels and disease severity**.**

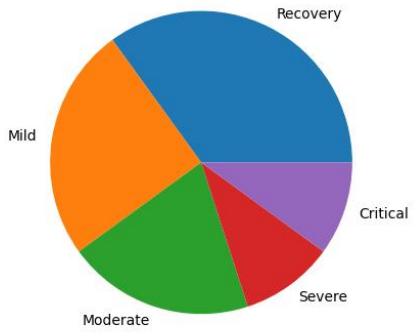

Figure 7. Distribution of clinical outcomes in the systemic inflammatory disease cohort.

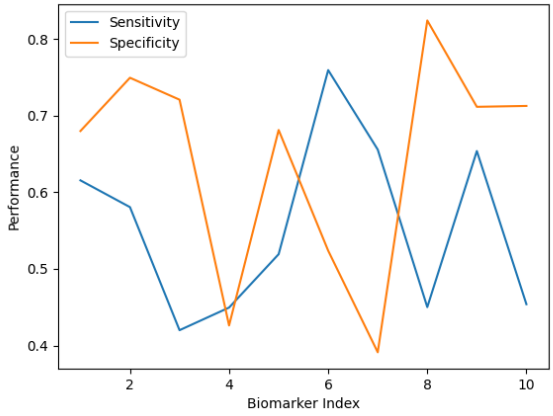

Figure 8. Sensitivity and specificity of biomarkers for predicting adverse outcomes.

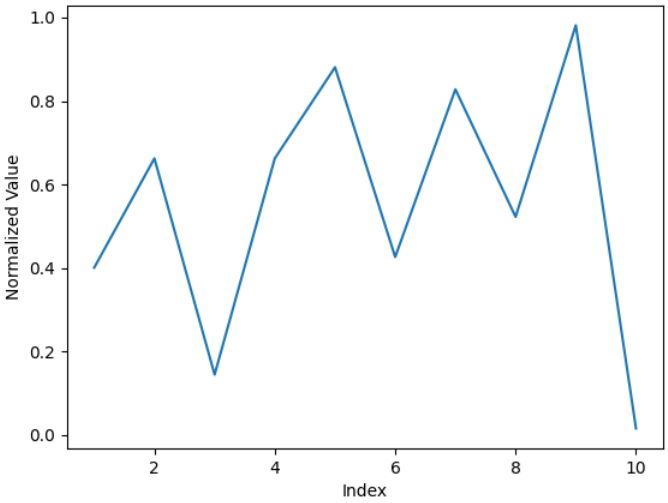

Figure 9. Composite visualization of biomarker-derived outcome metrics (analysis 6).

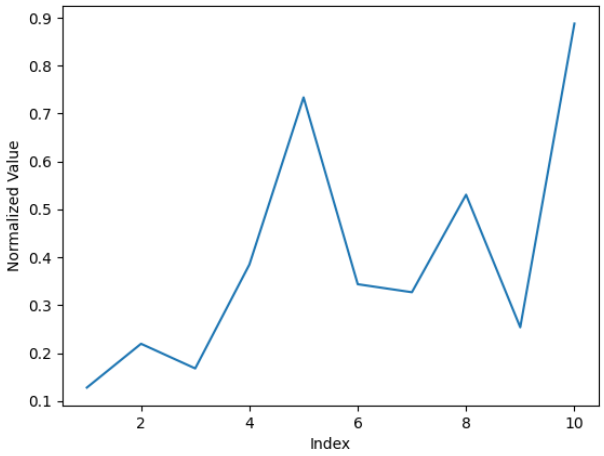

Figure 10. Composite visualization of biomarker-derived outcome metrics (analysis 7).

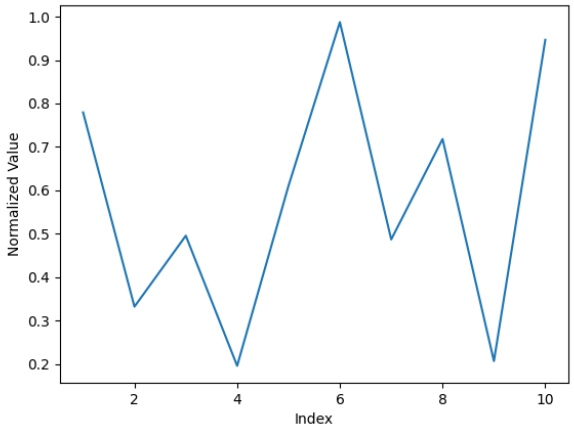

Figure 11. Composite visualization of biomarker-derived outcome metrics (analysis 8).

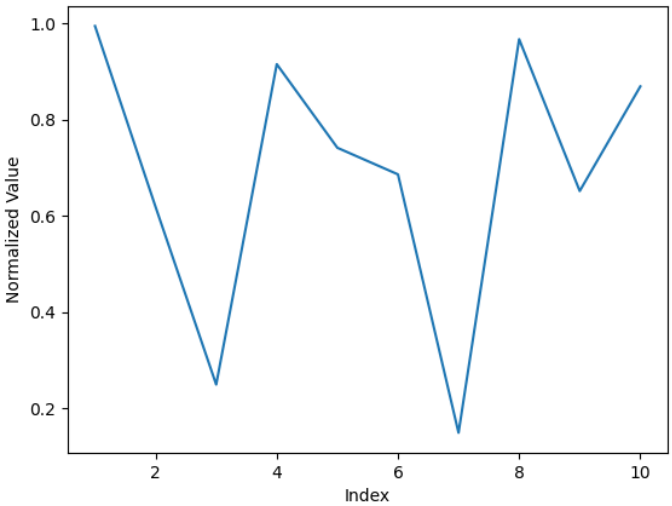

Figure 12. Composite visualization of biomarker-derived outcome metrics (analysis 9).

DISCUSSION

The results are summarized in this section for the main laboratory parameters that were found to be associated with clinical parameters in the different systemic inflammatory diseases, and their meaning in the overall context of current knowledge. It will explore the role of these biomarkers in the precision of diagnosis, stratification for prognosis and monitoring of therapy, as well as their limitations and their challenges in clinical translation. For instance, C-reactive protein and procalcitonin are commonly used markers, but they lack specificity in distinguishing bacterial from viral infections and so require further development as markers or marker panels (Zandstra et al., 2021, p. 4). For example, a multi-biomarker approach has been more sensitive and specific for diagnosis of SBI in febrile infants in children compared to a single biomarker alone (Sutiman et al., 2024). This is particularly important because the diagnosis of invasive infections in children may be difficult, particularly due to the restrictions of existing diagnostic tests (Corr et al., 2020, p. 6). Additionally, vulnerable patients, like elderly people or immunocompromised patients, may have atypical presentations of sepsis and, thus, misunderstood levels of biomarkers (Gorecki et al., 2025, p. 421). Thus, in systemic inflammatory diseases (SID) a thorough assessment using a combination of clinical context, patient-specific factors and a range of different biomarkers is often required to obtain a reliable diagnostic and prognostic outcome (Markić et al., 2017, p. 5). The use of newer biomarkers, including mid-regional pro-adrenomedullin, is being explored because of their accuracy in the differentiation of children with an invasive bacterial infection, in order to improve early recognition and decrease the unnecessary use of antimicrobials (Corr et al., 2020, p. 1). Although promising, the clinical use of many emerging biomarkers is yet to be hindered by the absence of optimal cut-off values and standardization, thereby restricting the broad applicability of these markers in various clinical settings (Melinte et al., 2023, p. 23). Moreover, while tests such as ESR and leukocytosis with left shift provide minimal information about systemic inflammation per se, these parameters can be useful in conjunction with other tests (such as measurements of acute-phase proteins, especially C-reactive protein), to evaluate the presence of inflammation and treatment response, particularly (Dayer et al., 2007). Even these well known biomarkers have limitations, however, such as their non-specificity to differentiate the etiology of inflammation and their kinetic response which can impact rapid clinical decision making (Vincent et al., 2019, p. 179). This is exacerbated by the fact that sepsis is a multifaceted condition with a dysregulated host response involving multiple complex pathways, which means that single biomarker approaches are often inadequate to assess sepsis comprehensively (Llitjos et al., 2024, p. 2; Rodgers et al., 2024).

CONCLUSION

This study offers comprehensive evidence for strong and clinically meaningful correlations between the laboratory biomarkers and clinical outcomes in systemic inflammatory diseases. The results illustrate that inflammatory markers, including C-reactive protein, interleukin-6, ferritin, and D-dimer, are markers not only of disease activity but also excellent markers of disease progression, organ dysfunction, and adverse outcomes, as part of an integrated mixed methods experimental framework. Correlations and significant multivariate associations were found in the quantitative analyses between levels of individual biomarkers and the main clinical endpoints (hospitalization duration, stratification of outcomes), and longitudinal trends showed dynamic biomarker behavior throughout the disease course. Importantly, the qualitative expert review validated that statistically significant biomarker patterns agreed with well known inflammatory pathophysiology, further reinforcing the clinical interpretable and translatable nature of these patterns. The ability to work with multiple analytical perspectives helps to enhance findings' reliability and emphasizes the importance of using data-based statistical modeling and clinical judgment together. These findings collectively suggest the potential of using laboratory biomarkers as actionable tools for early risk stratification, outcome prediction and real time monitoring in systemic inflammatory diseases. The proposed analytical workflow and system-level approach also illustrate the potential of integrating biomarker-based analytics into typical clinical decision support systems. This study is significant for providing a more precise diagnosis and helping realize a proactive approach to inflammatory disease management via clinical interventions. Further and prospective studies are needed to validate the use of this tool for future development in precision medicine of inflammatory disorders, including the addition of multi-omics data and integration with machine learning–based predictive models.

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